# Cardiac syndrome X in women: the role of oestrogen deficiency

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Cardiac syndrome X (CSX), defined as typical exertional chest pain, a positive response to stress testing, and normal coronary arteriograms, encompasses different pathogenic subgroups. Both cardiac and non-cardiac mechanisms have been suggested to play a pathogenic role, and it has been shown that the syndrome is associated with myocardial ischaemia in at least a proportion of patients. Radionuclide myocardial perfusion defects, coronary sinus oxygen saturation abnormalities and pH changes, myocardial lactate production and stress-induced alterations of cardiac high energy phosphate have been reported in CSX patients, suggesting an ischaemic origin for their symptoms. Microvascular abnormalities often caused by endothelial dysfunction appear to be responsible for myocardial ischaemia in these patients. CSX is more prevalent in women than in men, and the majority of women with CSX are peri- or post-menopausal. Thus oestrogen deficiency has been suggested to have a pathogenic role in CSX. Additional factors such as abnormal pain perception may also contribute to the genesis of chest pain in patients with angina and normal coronary angiograms. The management of this syndrome is difficult because of the heterogeneity of pathogenic mechanisms and uncertainties as to its origin. This article discusses the problem of CSX in women, the potential pathogenic role of oestrogen deficiency, and practical clinical management.

Chest pain suggestive of myocardial ischaemia despite normal coronary arteriograms, often referred to as cardiac syndrome X (CSX), is a relatively common diagnosis. It has been reported that approximately 30% of patients undergoing coronary angiography for the assessment of coronary artery disease have normal or minimally diseased coronary arteries.[1] Characteristically, CSX is more common in women than in men and the observation that women with CSX are often menopausal seems to indicate that oestrogen deficiency may have a pathogenic role in this condition. CSX is diagnosed in the presence of typical exercise-induced angina pectoris, transient ischaemia-like ST segment depression during pain, and angiographically normal coronary arteries.[1] The character and location of the chest pain, its triggering factors and the occurrence of ST segment shifts during chest pain are similar to those seen in patients with coronary artery disease (CAD).[1–3] However, although in the majority of patients the episodes of ST segment depression are associated with tachycardia, not infrequently CSX patients have ischaemic episodes that are not preceded by an increased heart rate.[1–3] Albeit uncommon, ST segment elevation similar to that seen in patients with Prinzmetal's variant angina has been reported in CSX patients, caused by microvascular spasm. Quite often myocardial perfusion defects are detected in CSX patients due to either heterogeneous myocardial perfusion or true myocardial ischaemia.[4] Patients with coronary artery spasm, cardiomyopathy, and left ventricular hypertrophy frequently present with chest pain in the absence of obstructive CAD, but these conditions are usually excluded from the diagnosis of CSX. Despite its good prognosis CSX represents a major clinical challenge. This article summarises the clinical dilemmas associated with CSX in women and discusses management strategies.

## PATHOGENESIS

### Myocardial ischaemia and microvascular dysfunction

CSX results from a variety of pathogenic mechanisms that clinically manifest with typical chest pain suggestive of coronary atheroma. Myocardial ischaemia, caused by a reduced coronary dilatory capacity of the coronary microcirculation, an increased coronary resistance, or both (''microvascular angina''), appears to be one of these mechanisms. Studies using radionuclide imaging techniques (figs 1 and 2) have objectively shown the presence of transient abnormalities of myocardial perfusion in approximately 30% of CSX patients.[5 6] Recently, we observed a correlation between systemic endothelial dysfunction and thallium defects in CSX patients,[6] a finding that expands previous observations of Zeiher *et al*.[7] The true meaning of thallium perfusion defects in CSX is speculative as they may represent myocardial hypoperfusion, an impaired performance of the sodium-potassium (Na-K) pump without myocardial ischaemia, or heterogeneous myocardial perfusion.[8–11] Using myocardial-perfusion cardiovascular magnetic resonance imaging Panting *et al*[12] showed a reduction in the subendocardial to subepicardial perfusion reserve ratio in CSX patients compared to controls. Sympathetic activation could be responsible for coronary arteriolar vasoconstriction in the subendocardial vessels, which, in turn, could result in relative myocardial hypoperfusion. Although speculative, this could explain the occurrence of chest pain and abnormal perfusion images observed in syndrome X, without the need to invoke myocardial ischaemia. Using 31-phosphorus nuclear magnetic resonance, Buchthal *et al*[13] assessed 35 women hospitalised for angina-like chest pain but without CAD. Twenty per cent of these women showed an abnormal metabolic response to handgrip exercise stress test, compatible with myocardial ischaemia. The technique used in this study directly measures high-energy phosphates in the myocardium and, therefore, provides direct metabolic evidence of ischaemia. Buffon *et al*[14] also showed myocardial ischaemia in both CAD and CSX patients following atrial pacing.

**Abbreviations:** CAD, coronary artery disease; CRP, C-reactive protein; CSX, cardiac syndrome X; ET-1, endothelin-1; NO, nitric oxide; TENS, transcutaneous electrical nerve stimulation

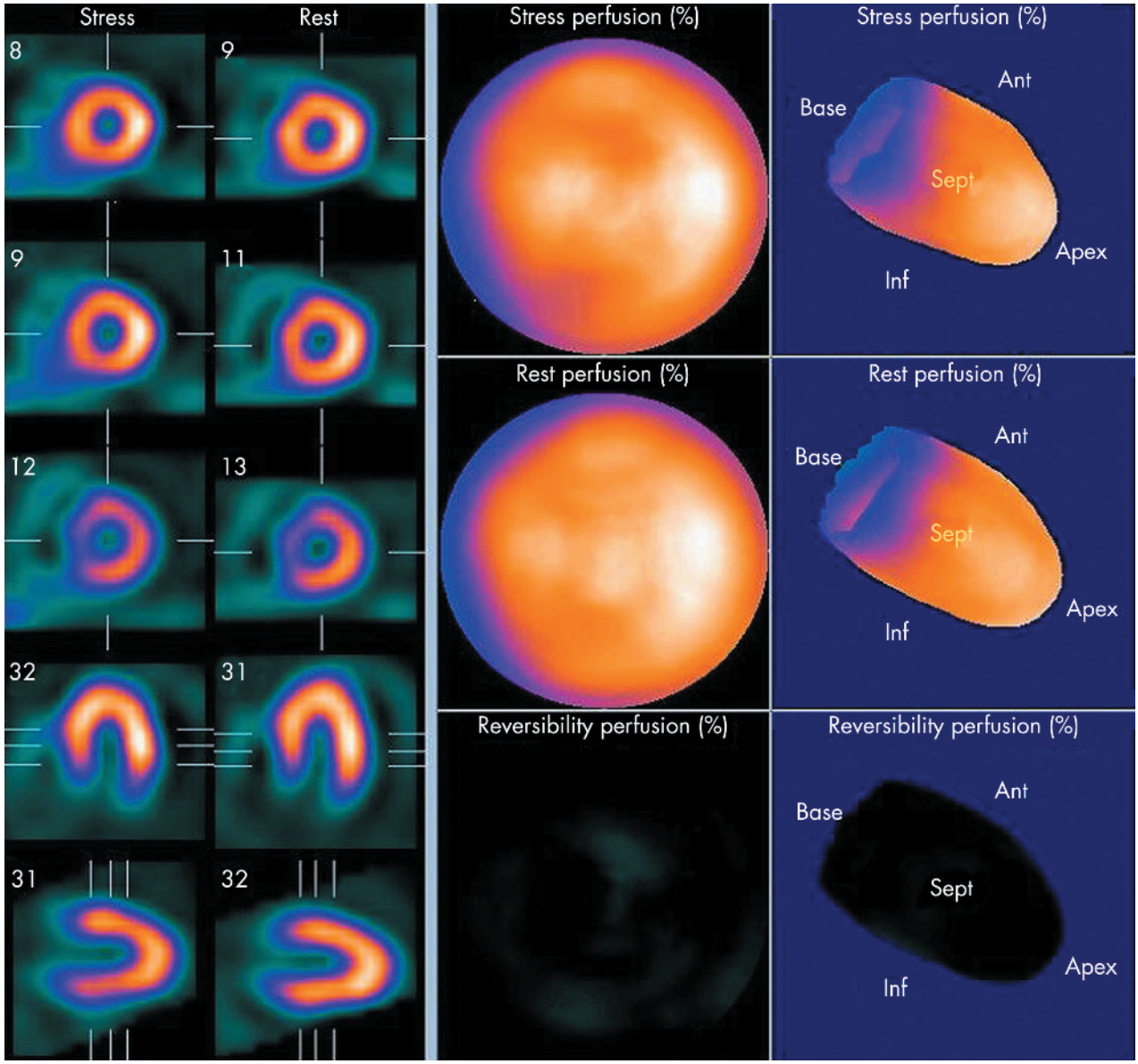


**Figure 1** Sixty year old female, presented with typical chest pain and a positive exercise test. She underwent myocardial perfusion scintigraphy (MPS). Above are selected tomographic images and polar plots acquired after adenosine stress and following a rest injection of a 99m-Tc myocardial perfusion tracer. Images show normal myocardial perfusion after stress and rest, confirmed by the polar plots and the absence of any reversible perfusion on the subtraction image (lower right image).

Myocardial ischaemia, however, can be detected objectively in only a small proportion of CSX patients using conventional techniques. In patients with microvascular angina it has been speculated that endothelial dysfunction can be the cause of the abnormal microvascular responses.[15] An imbalance between vasodilator forces such as nitric oxide and vasoconstrictor ones such as endothelin-1 (ET-1) may have a causative role in CSX. Kaski *et al*[16] reported for the first time that plasma ET-1 values are significantly higher in patients with CSX compared to healthy controls. More recently, Kolasinska *et al*[17] showed that CSX is associated with a significantly lower basal concentration of nitric oxide (NO) and lower basal NO/ET-1 ratio. These findings support the hypothesis that endothelial dysfunction resulting in a reduced availability of NO may cause microvascular dysfunction and CSX. Data from our unit[18] suggest that increased circulating ET-1 concentrations are associated with impaired coronary microvascular dilatation in response to pacing, providing further support to the hypothesis that abnormal ET-1 concentrations may contribute to the pathogenesis of CSX. Insulin resistance has been also shown to be associated with endothelial dysfunction and microvascular angina,[19–21] and inflammation may also have a pathogenic role in this context. We showed that increased C-reactive protein (CRP) concentrations are related to symptom activity and myocardial ischaemia in patients with chest pain and normal coronary angiograms.[22]

## Oestrogen deficiency and endothelial dysfunction

The finding that post-menopausal women represent the prevailing group among CSX patients suggests that oestrogen deficiency may play a pathogenic role.[23] During the menopause healthy women show an impairment of endothelial function,[24] and the administration of exogenous oestradiol increases peripheral blood flow in these women.[25] Postmenopausal women with CSX have an impaired

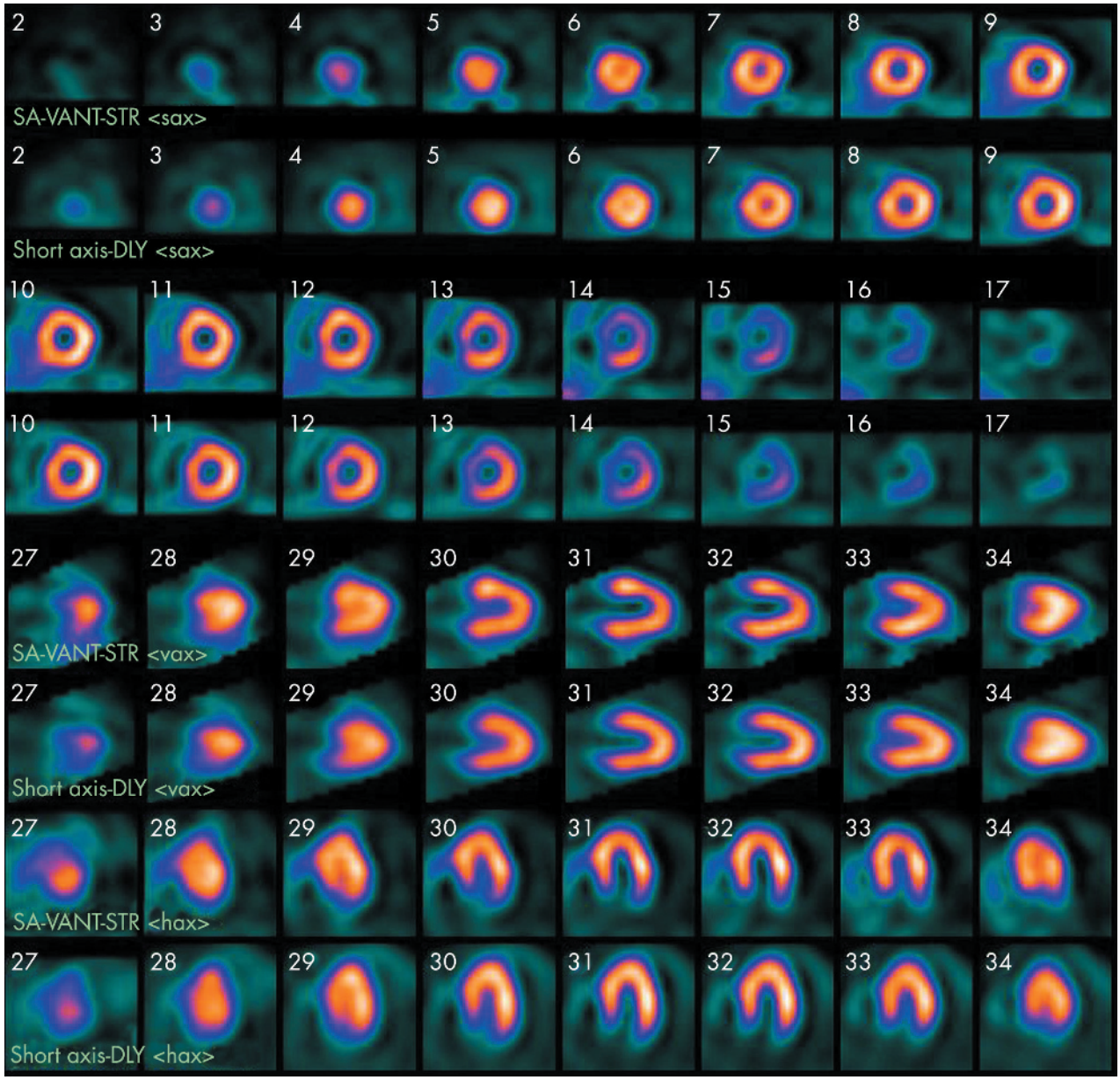


**Figure 2** Tomographic myocardial perfusion images, after adenosine stress and rest, following injection of radioactive 99m-Tc tracer showing normal myocardial perfusion, throughout the left ventricular myocardium, in a female with symptoms suggestive of angina. Prognosis from this study indicates that there is no significant coronary obstruction and the likelihood of coronary events in the near future (4 to 5 years) is very low, <1% per annum.

endothelial function, which is improved by the administration of oestrogen.[26] Whether the beneficial effect of oestrogen is related to its direct vasodilating effects on the coronary arteries or an endothelium-dependent effect[27–29] is not known. Oestrogen receptors are expressed in cells of the cardiovascular system and modulate vasomotor tone as a result of a rapid vasodilator effect, which occurs within minutes of oestrogen administration, and is independent of gene expression, and/or longer term effects on the vascular wall, which are dependent on the expression of specific genes.[30]

## Oestrogen and modulation of nociception

Endorphin release is activated by pain, and other stimuli. Activation of endorphin release is associated with a reduced pain perception and an attenuation of pain-related emotions (anti-nociception).[31] Changes in women's oestrogen concentrations, like those that occur during the menstrual cycle, or during pregnancy, modulate the natural ability of the brain to suppress pain. When oestrogen values are high, the brain's natural antinociceptive system responds in a stronger fashion to painful stimuli, releasing endorphins or enkephalins that dampen the pain signals received by the brain.[31 32] When oestrogen is low, the system does not control pain as efficiently.[32] Mu-opioid receptors are responsible for antinociception, and can be found throughout the brain, but are mainly concentrated in areas known to influence physical and emotional responses to stressors, including pain. Natural endorphins and painkillers bind to these receptors and the effect is a reduction in the perception of pain and the response to it.[31]

In 2002, the Zubieta team reported for the first time that some of the differences between individuals in response to pain are governed by the mu-opioid system.[33] In the study,

men scanned before and during jaw pain showed increases in endorphin release in certain brain areas during pain. Women in the study, however, showed a reduction in endorphin release during pain and also reported feeling more intense pain, and more pain-related negative emotions, than the men. Interestingly all the women were studied at a time in their menstrual cycle when concentrations of oestrogen and progesterone were at their lowest (early follicular phase). In a more recent study, healthy women were scanned during their early follicular phase, and the scan was repeated during that same phase a month later after treatment with an oestrogen-releasing skin patch for a week. Scans made without any painful stimulation showed that when the oestrogen concentration was high, the number of mu-opioid receptors increased in the brain. When the painful stimulus was applied, the women under high-oestrogen conditions showed a pronounced increase in their ability to release endorphins and activate the receptors.[34]

### Hormone replacement therapy

Reduced oestrogen production can lead to vasomotor instability and it has been shown that the acute administration of transdermal oestrogen improves endothelium-dependent coronary vasomotion.[26 35] Contradictory results, however, have been published regarding the efficacy of transdermal oestrogen to improve exercise induced ST segment depression, and chest pain during daily life.[36 37] The alleviation of chest pain by oestrogen seen in some studies does not necessarily imply an anti-ischaemic action.[37] 17β-oestradiol attenuates adenosine production and modulates its actions.[36 37] Despite the convincing evidence for a potential pathogenic role in CSX in women, as discussed previously, in clinical practice oestrogen replacement therapy per se rarely results in a significant improvement of ischaemic ECG changes. Type of oestrogen, variable combinations of oestrogen and progestogens, and timing of administration may be responsible for the lack of more clear cut results with the use of these agents. Different pathogenic mechanisms operating in different patients may also be responsible for the lack of efficacy of oestrogen in some trials but not in others. However, oestrogen administration often is a useful adjunctive therapy in selected subgroups of women with CSX, particularly those with angina symptoms associated with variations in hormonal values.

The use of oestrogen therapy is not without problems at present,[38] as shown by recent randomised, controlled clinical trials. Hormone replacement therapy increases the risk of cardiovascular disease, and of breast cancer. Hence, although hormonal therapy has the potential to confer cardiovascular protection, it can also cause cardiovascular harm.[38] A scientific review conducted for the US Preventative Services Task Force[38] assessed risks and benefits of this treatment and found the following: an increased risk of coronary events, stroke and venous thromboembolism (risk highest in the first year); an increased risk of breast cancer (associated with duration of treatment); an increased risk of endometrial cancer and cholecystitis; protection against osteoporotic complications; a decreased risk for colon cancer; and cognition improvement in women with menopausal symptoms. Routine post-menopausal hormonal therapy is not currently advised for the prevention of chronic conditions, and similar recommendations could be made for cardiac syndrome patients. In specific cases where a direct link has been established between symptoms and changes in oestrogen concentrations, substitutive treatment may be useful. However, women should be informed on an individual basis about their specific risk-benefit profiles. The design of future oestrogen replacement trials in women with CSX should include these patients in whom a relation has been established between angina symptoms and hormonal concentrations.

### Abnormal pain perception

Abnormalities in pain perception, with an increased sensitivity to painful stimuli, are commonly found in patients with chest pain and normal coronary angiograms.[39 40] The cause of the increased chest pain perception in these patients has not been completely elucidated but recent studies have shed light into the possible mechanisms. Alterations in the potassium and adenosine ionic pumps have been proposed to explain the reduced pain threshold in CSX,[41 42] and perhaps more importantly, abnormalities in the modulation of pain perception by the central nervous system appear to play an important role. Rosen *et al*[43] showed that the occurrence of chest pain was associated with greater and more extensive cortical activation, especially the right insula, in CSX patients compared to controls. Right anterior insular activity during high dose dobutamine infusion was higher in CSX patients compared to both CAD and control patients; this suggests that activation of the right insula, an area of the brain that receives most of the cardiopulmonary input, has a significant role in the increased pain perception in CSX.[43–45] The ''gate theory'' of pain perception[46] has been proposed to explain the intriguing findings. Healthy individuals have a continuous stream of afferent stimuli from the heart, secondary to increased cardiac work, which reach the thalami but not the cortex; hence no pain perception takes place. In patients with CAD, if the increased cardiac work causes myocardial ischaemia, the stream of afferent stimuli is stronger and overcomes the filtering ability of the thalamus, which will therefore allow pain signals to reach the cortex and therefore pain will be perceived by the patient (angina pectoris). However, in patients with CAD who have silent myocardial ischaemia, there is an altered handling of afferent signals from the heart at the central level (''overactive gate'') that blocks the occurrence of chest pain in these patients. CSX patients, on the other hand, may have an ineffective thalamic ''gate'' that allows excessive cortical activation by afferent stimuli, thus resulting in increased pain perception.[45]

The hypothesis of an altered somatic and visceral perception of pain in CSX has therapeutic implications. Imipramine has analgesic properties[47] and has been assessed for the relief of chest pain in CSX patients.[48 49] Imipramine significantly reduces daily-life chest pain.[48 49] Transcutaneous electrical nerve stimulation (TENS) indirectly delivers low voltage electrical impulses onto the spinal cord following stimulation of A-β fibres via the skin. TENS has been shown to be useful for the treatment of a variety of chronic pain conditions including chronic stable angina pectoris,[50] but results are not universally positive. Spinal cord stimulation, which involves the direct electrical stimulation of the spinal cord, requires the percutaneous introduction of an electrode into the epidural space, and the attachment of the electrode to an implanted pulse generator. Beneficial reports have been published with this tool in small CSX patient series,[51 52] but studies in larger numbers of patients are needed.

## CONCLUSIONS

The high prevalence of post-menopausal women in CSX suggests that oestrogen deficiency may play a pathogenic role, as oestrogen modulates endothelial function and pain perception. Myocardial ischaemia, associated with microvascular dysfunction, is one of the possible pathogenic mechanisms underlying chest pain with normal coronary arteriograms in women.[53] Oestrogen replacement therapy is not without problems at present, but in selected patients it may represent a useful adjunct to other therapeutic measures.

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